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Proposed Registration Decision PRD2011-14

Extract of *Reynoutria sachalinensis*

(publié aussi en français)

23 December 2011

This document is published by the Health Canada Pest Management Regulatory Agency. For further information, please contact:

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Canada

ISSN: 1925-0878 (print)
1925-0886 (online)

Catalogue number: H113-9/2011-14E (print version)
H113-9/2011-14E-PDF (PDF version)

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Overview

Proposed Registration Decision for Extract of *Reynoutria sachalinensis*

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of *Reynoutria sachalinensis* Bioprotectant Technical and Regalia Maxx Biofungicide Liquid Concentrate, containing the technical grade active ingredient extract of *Reynoutria sachalinensis*, to suppress a variety of diseases on field and greenhouse edible crops and ornamentals.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

This Overview describes the key points of the evaluation, while the Science Evaluation section provides detailed technical information on the human health, environmental and value assessments of *Reynoutria sachalinensis* Bioprotectant Technical and Regalia Maxx Biofungicide Liquid Concentrate.

What Does Health Canada Consider When Making a Registration Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable[1] if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its proposed conditions of registration. The Act also requires that products have value[2] when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (e.g., children) as well as organisms in the environment (e.g., those most sensitive to environmental contaminants). These methods and policies also consider the nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the PMRA's website at healthcanada.gc.ca/pmra.

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1 "Acceptable risks" as defined by subsection 2(2) of the *Pest Control Products Act*.

2 "Value" as defined by subsection 2(1) of the *Pest Control Products Act*: "the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (*a*) efficacy; (*b*) effect on host organisms in connection with which it is intended to be used; and (*c*) health, safety and environmental benefits and social and economic impact."

Before making a final registration decision on extract of *Reynoutria sachalinensis*, the PMRA will consider all comments received from the public in response to this consultation document[3]. The PMRA will then publish a Registration Decision[4] on extract of *Reynoutria sachalinensis*, which will include the decision, the reasons for it, a summary of comments received on the proposed final registration decision and the PMRA's response to these comments.

For more details on the information presented in this Overview, please refer to the Science Evaluation section of this consultation document.

What Is Extract of *Reynoutria sachalinensis*?

The active ingredient is a plant extract from the giant knotweed plant (*Reynoutria sachalinensis*). When sprayed on plants, the extract activates Induced Systemic Resistance (ISR), an internal defence mechanism in plants that prevents growth of certain plant pathogens. The reaction within the plant suppresses diseases on ornamental plants, wheat, cucurbits, tomatoes, grapes and strawberries.

Health Considerations

Can Approved Use of Extract of *Reynoutria sachalinensis* Affect Human Health?

Extract of *Reynoutria sachalinensis* is unlikely to affect human health when used according to label directions.

Potential exposure to extract of *Reynoutria sachalinensis* may occur when handling and applying the product or when people enter a freshly treated site. When assessing health risks, two key factors are considered: the levels where no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (e.g., children and nursing mothers). Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

The technical grade active ingredient, extract of *Reynoutria sachalinensis*, is anticipated to be of low acute toxicity by the oral, dermal and inhalation routes and minimally irritating to eyes and skin, and not a skin sensitizer. There is no information available in the published scientific literature that suggests extract of *Reynoutria sachalinensis* is carcinogenic, genotoxic, neurotoxic or is a developmental/reproductive toxicant. Moreover, the plant has long been used as a food ingredient and in medicinal products, in some parts of the world, with a history of safe consumption.

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3 "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

4 "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.

The end-use product is of low acute toxicity by oral, dermal, and inhalation routes, is moderately irritating to eyes, mildly irritating to skin, and is not a dermal sensitizer. Due to the irritation potential of the end-use product and the likely exposure of workers and commercial applicators to it via inhalation and contact with skin and eyes, personal protective equipment, precautionary statements, and a restricted-entry statement are required on the label to mitigate any exposure concerns.

Residues in Water and Food

Dietary risks from food and water are not of concern.

As part of the assessment process prior to the registration of a pesticide, Health Canada must determine whether the consumption of the maximum amount of residues that are expected to remain on food products when a pesticide is used according to label directions, will not be a concern to human health. This expected maximum amount of residues is then legally established as a maximum residue limit (MRL) under the *Pest Control Products Act* for the purposes of the adulteration provision of the *Food and Drugs Act*. Health Canada sets science-based MRLs to ensure the food Canadians eat is safe.

Reynoutria sachalinensis has long been used as a food item and also consumed for its medicinal values in some parts of the world with no reported adverse effects. There is reasonable certainty that no harmful effects will occur from dietary and drinking water residue exposure to extract of *Reynoutria sachalinensis* from the use of Regalia Maxx Biofungicide Liquid Concentrate. At the time of harvest, the residue level of crops treated with *Reynoutria sachalinensis* is not expected to exceed the natural levels in consumed food or medicinal products. Therefore, no crop residue data are needed and the establishment of an MRL will not be required by PMRA.

While good hygiene practices, such as washing food produce prior to consumption, are not considered in the assessment for the registration of a food-use pesticide, they are recommended as any remaining residues are likely to be reduced by washing and possible cooking of the treated crop before eating.

Occupational Risks From Handling Extract of *Reynoutria sachalinensis*

Occupational risks are not of concern when extract of *Reynoutria sachalinensis* is used according to label directions, which include protective measures.

Occupational exposure to individuals mixing, loading, or applying Regalia Maxx Bioprotectant Liquid Concentrate is not expected to result in unacceptable risk when the product is used according to label directions.

Precautionary (e.g., wearing of personal protective equipment) and hygiene statements on the end-use product label aimed at mitigating exposure are considered adequate to protect individuals from any unnecessary risk due to occupational exposure.

Environmental Considerations

What Happens When Extract of *Reynoutria Sachalinensis* is Introduced into the Environment?

The active ingredient, extract of *Reynoutria sachalinensis*, is a naturally occurring constituant of the plant, *Reynoutria sachalinensis* (a.k.a. giant knotweed). As such, it is expected to break down completely within a relatively short period of time and, therefore, will not be persistent in the environment. Extract of *R. sachalinensis* is not expected to cause adverse effects to non-target terrestrial and aquatic organisms.

Value Considerations

What Is the Value of Regalia Maxx Biofungicide Liquid Concentrate?

Regalia Maxx Biofungicide Liquid Concentrate is a biological fungicide that suppresses diseases on a wide variety of plants.

By activating plant defences, Regalia Maxx Biofungicide Liquid Concentrate elicits the plant to defend itself against multiple fungal and bacterial pests through the accumulation of phenolic compounds. Preventative application of this product will suppress plant diseases and is most appropriate for use under low disease pressure. Resistance to the active ingredient is unlikely to develop. This product has the potential to become an integral part of an Integrated Pest Management (IPM) program, especially for organic growers.

Measures to Minimize Risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

The key risk-reduction measures being proposed on the label of Regalia Maxx Biofungicide Liquid Concentrate to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

Human Health

The statements, "WARNING: EYE IRRITANT" and "CAUTION: SKIN IRRITANT" are required on the principal display panel.

The existing or additional precautionary statements on the secondary display panel of the label include, "Causes moderate eye irritation, May irritate skin, may cause irritation of the respiratory tract, DO NOT get in eyes, avoid contact with skin or clothing, and avoid inhaling/breathing spray mist."

Mixer/Loader/Applicator and related workers are required to wear a long-sleeved shirt, long pants, shoes plus socks, waterproof gloves, and goggles or face shield when handling, mixing/loading or applying the product, and during all clean-up/repair activities.

The label is required to include the restricted-entry statement, "Do not re-enter or allow entry into treated areas until the spray is dried."

Applicators/workers in greenhouses must wear a NIOSH approved respirator, proper protective clothing, shoes plus socks, water-proof gloves, and protective eye-wear when using high pressure sprayers or when entering a treated area before thorough ventilation and clearing of spray mist.

Keep unprotected persons out of the treated areas in a greenhouse for the duration of the treatment period

Allow entry or re-entry to greenhouse only after thorough ventilation and spray mist or fog has cleared and the treated surface has dried.

Environment

No mitigative measures are required for the proposed use of Regalia Maxx Biofungicide Liquid Concentrate.

Next Steps

Before making a final registration decision on extract of *Reynoutria sachalinensis*, the PMRA will consider all comments received from the public in response to this consultation document. The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document. Please forward all comments to Publications (contact information on the cover page of this document). The PMRA will then publish a Registration Decision, which will include its decision, the reasons for it, a summary of comments received on the proposed final decision and the Agency's response to these comments.

Other Information

When the PMRA makes its registration decision, it will publish a Registration Decision on extract of *Reynoutria sachalinensis* (based on the Science Evaluation section of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa).

Science Evaluation

Extract of *Reynoutria sachalinensis*

1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

Active substance	Extract of *Reynoutria sachalinensis*
Function	Fungicide
Chemical name	
1. **International Union of Pure and Applied Chemistry (IUPAC)**	Not applicable
2. **Chemical Abstracts Service (CAS)**	Not applicable
CAS number	Not applicable
Molecular formula	Not applicable
Molecular weight	Not applicable
Structural formula	Not applicable
Purity of the active ingredient	100% nominal

1.2 Physical and Chemical Properties of the Active Ingredients and End-Use Product

Technical Product – *Reynoutria sachalinensis* Bioprotectant Technical

Property	Result
Colour and physical state	Olive green, brown and cream solid
Odour	Not applicable
Melting range	Not applicable
Boiling point or range	Not applicable
Density	0.135 ± 0.004 g/mL
Vapour pressure at 20°C	Not applicable
Henry's law constant at 20°C	Not applicable
Ultraviolet (UV)-visible spectrum	Not applicable
Solubility in water at 20°C	Not applicable

Property	Result
Solubility in organic solvents at 20°C (g/100 mL)	Not applicable
n-Octanol-water partition coefficient (K_{ow})	Not applicable
Dissociation constant (pK_a)	Not applicable
Stability (temperature, metal)	Not applicable

End-Use Product – Regalia Maxx Biofungicide Liquid Concentrate

Property	Result
Colour	Not applicable
Odour	Not applicable
Physical state	Liquid
Formulation type	Liquid
Guarantee	20% nominal
Container material and description	Polyvinyl chloride (PVC) bottles and jugs 1 to 50 L
Density	1.123 g/mL
pH of 1% dispersion in water	5-6
Oxidizing or reducing action	The EP is not expected to have any oxidizing or reducing properties.
Storage stability	Not applicable
Corrosion characteristics	The EP is not expected to be corrosive.
Explodability	The EP is not expected to be explosive.

1.3 Directions for Use

Regalia Maxx Biofungicide Liquid Concentrate should be applied as a preventative treatment to all supported crops at rates between 0.125% and 0.25% v/v in sufficient water volume to provide thorough coverage (400-1500 L/ha). Applications should begin at the first sign of disease or when conditions are conducive to disease development. Repeat applications should be made between 10 and 14 days apart.

1.4 Mode of Action

Extract of *Reynoutria sachalinensis* induces chemical elicitors of the target plant's defence mechanisms involved in ISR. The elicitors induce accumulation of phenolic compounds (phytoalexins) which display antifungal activity. The reaction is not systemic, but some translaminar protection has been observed. Repeat applications are required to maintain systemic resistance. Plant resistance induction occurs in one to two days. Light is required for best results.

2.0 Methods of Analysis

2.1 Methods for Analysis of the Active Ingredient

A non-validated analytical method was provided for the analysis of one of the compounds present in the active ingredient and was assessed to be acceptable for the determination.

2.2 Method for Formulation Analysis

Based on the nature of the product this requirement is waived.

2.3 Methods for Residue Analysis

Not applicable.

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

A detailed review of the toxicological database for the extract of *Reynoutria sachalinensis* and its associated end-use product, Regalia Maxx Biofungicide Liquid Concentrate, was conducted by PMRA. The database consisted of acute toxicity and mutagenicity studies and rationales to waive certain study requirements. The scientific quality of the data and information submitted is acceptable and the database is sufficiently complete to define the majority of the toxic effects that may result from exposure when this pest control product is used according to label directions.

All the submitted acute toxicity studies on the technical grade active ingredient were conducted with ground dried plant material of *Reynoutria sachalinensis* instead of the alcoholic extract of the ground dried plant material which is used to formulate Regalia Maxx Biofungicide Liquid Concentrate. These studies were accepted as the ethanolic extract and the parent plant material are unlikely to have significantly different toxicology profiles.

Based on the results with the ground dried plant material, as summarized in Appendix I, Table 1, the extract of *Reynoutria sachalinensis* is expected to be of low acute toxicity by the oral and dermal routes. The request to waive inhalation toxicity testing was accepted based on the anticipated low inhalation toxicity of the plant extract and results from the inhalation study on the end-use product, which indicated low toxicity. The plant extract is expected to be minimally irritating to eyes, minimally irritating to skin, and not a dermal sensitizer.

Regalia Maxx Biofungicide Liquid Concentrate is of low acute toxicity by oral, dermal, and inhalation routes, moderately irritating to eyes, mildly irritating to skin, and is not a dermal sensitizer (see Appendix I, Table 2). Due to the potential for mucosal irritation, the end-use product is likely to result in irritation of the respiratory tract.

Bacterial reverse mutation assays and mammalian micronucleus tests were submitted for the ethanolic plant extract (see Appendix I, Table 3). The bacterial reverse mutation assay (*Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, and tester strain *E. coli* WP2 uvrA) on the extract showed positive results with an increase in revertant colonies in tester strain TA 1537 in the presence of S-9 metabolic activation. The mammalian micronucleus test on the extract showed negative results with no induction of structural and/or numerical chromosomal damages in the immature erythrocytes of the mouse.

The positive results seen in the bacterial reverse mutation assay for one strain of *S. typhimurium* with the extract do not necessarily indicate a potential genotoxic risk to mammalian systems. Furthermore, bacterial mutation assays using other strains of *S. typhimurium* and *E. coli* were negative, as was a mammalian micro-nucleus test. Therefore, it is unlikely that the plant extract is genotoxic.

The applicant's requests to waive short-term oral, short-term dermal, and prenatal developmental toxicity studies were accepted by the PMRA. *Reynoutria sachalinensis* is commonly found in some parts of the world, including Canada, and has a long history of use as a food item and as an ingredient in medicinal products without any reports of adverse effects in the publicly available literature. There is no evidence to suggest that it (or its ethanolic extract) would be carcinogenic, genotoxic, neurotoxic or a developmental/reproductive toxicant. Consequently, no short-term and chronic toxicity studies are required to complete the human health risk assessment.

3.2 Occupational Exposure and Risk Assessment

3.2.1 Use Description Scenario

Regalia Maxx Biofungicide Liquid Concentrate is to be used as a preventative treatment of diseases in field and greenhouse grown ornamental and edible crops. The proposed greenhouse uses include application to ornamental plants, cucurbits, and tomatoes using a variety of spraying apparatuses, performed manually or by automation. The spraying equipment generally used in a greenhouse includes: heavy duty hydraulic high volume sprayer, backpack sprayer, boom sprayers mounted on rails, mechanical aerosol generators (foggers), mist blowers, autofoggers, etc. For field applications, the end-use product is to be applied by foliar airblast, horizontal boom sprayer, or vineyard spraying.

The proposed rate of application is 0.125%–0.25% v/v of product in 400–1000 L water per hectare. The higher volume is for thorough coverage of larger sized crops and extensive foliage. The label recommends agitation when preparing the spray solution if mechanical mixing is available and to use an anionic wetting agent at 0.02% v/v of the final water volume. Re-application is proposed every seven to fourteen days as needed.

3.2.2 Mixer, Loader and Applicator Exposure and Risk Assessment

The use of Regalia Maxx Biofungicide Liquid Concentrate may result in exposure to mixers, loaders, and applicators, as well as those responsible for clean-up and maintenance activities. Workers will be primarily exposed by inhalation, dermal and ocular routes. Due to the potential for mucosal irritation, inhalation of the end-use product is likely to result in irritation of the respiratory tract. Inhalation exposure to applicators from spray mist and dermal exposure from post-application contact to freshly treated wet surfaces are also likely. Occupational exposure to the end-use product will be minimal if workers follow label recommendations. The label has a number of exposure reduction statements (e.g., wearing of personal protective equipment) to protect mixers, loaders and applicators against any unnecessary risk from exposure. Also, the Regalia Maxx Biofungicide Liquid Concentrate label instructs that handlers and applicators avoid contacting skin, eyes, and clothing with the spray solution.

For greenhouse application, the major occupational concern is from inhalation exposure for applicators when they use high pressure equipment and are exposed to fog and spray mist. As a protective measure, when using high pressure sprayers, applicators are required to wear a NIOSH approved respirator, proper protective clothing, shoes plus socks, water-proof gloves, and a protective eye-wear.

Significant risk from exposure to Regalia Maxx Biofungicide Liquid Concentrate for the mixer, loader and applicator, as well as those responsible for clean-up, maintenance and repair activities is not anticipated due to the low toxicity of the active ingredient and formulation, and reduced occupational exposure when label directions are followed.

3.2.3 Bystander Exposure and Risk Assessment

As the commercial application involves only authorized personnel, bystander exposure is expected to be negligible when the end-use product is used according to the label directions. To avoid bystander exposure in greenhouses, the end-use product label must state that unprotected persons should be kept out of the greenhouses for the duration of the treatment period.

3.2.4 Post-Application Exposure

Post-application exposure is possible when people enter the treated area soon after the application. The primary route of exposure for re-entry workers/individuals is dermal from contact with freshly treated surfaces. As the applied spray material is a dilute solution, post-application exposure is not expected to be of concern when re-entry to freshly treated areas is restricted until sprays have dried, as has been specified on the label. In greenhouses, post-application exposure is of concern when workers or people re-enter a treated area immediately after application and are exposed by inhalation routes to spray mist/fog if the area is not thoroughly ventilated or sufficient time was not given to let the suspended particles settle out of the air. To mitigate such potential exposures, worker entry/re-entry to treated areas are thoroughly ventilated or entry/re-entry should only be permitted when personal protective

equipment consisting of a NIOSH approved respirator, proper protective clothing, shoes plus socks, water-proof gloves, and a protective eye-wear is used.

3.3 Dietary Exposure and Risk Assessment

3.3.1 Food

Regalia Maxx Biofungicide Liquid Concentrate is proposed for use as a foliar spray on food crops (cereal grains, cucurbits, fruiting vegetables, leafy vegetables, grapes, strawberry, and stone fruits). As there is no pre-harvest interval proposed, food residues are possible from the application of the end-use product. However, because of the low proposed application rates coupled with the anticipated low persistence of the plant extract in the environment due to its susceptibility to environmental degradation by biological, physical, and/or chemical processes, the PMRA anticipates the use of Regalia Maxx Biofungicide Liquid Concentrate will result in residue levels that will not be of toxicological concern. There is reasonable certainty that no harmful effects will result from dietary exposure to residues of ethanolic extract of *Reynoutria sachalinensis* in the general population and potentially sensitive subpopulations, including infants and children.

Furthermore, while good hygiene practices, such as washing food produce prior to consumption, are not considered in the assessment for the registration of a food-use pesticide, they are recommended as any remaining residues are likely to be reduced by washing and possible cooking of treated crop before eating.

3.3.2 Drinking Water

Drinking water exposure to residues from the application of the end-use product is expected to be negligible because of the low rates of application and the anticipated non-persistence of the plant extract in the environment.

3.3.3 Maximum Residue Limits (MRLs)

As part of the assessment process prior to the registration of a pesticide, Health Canada must determine whether the consumption of the maximum amount of residues that are expected to remain on food products when a pesticide is used according to label directions, will not be a concern to human health. This maximum amount of residues expected is then legally established as a maximum residue limit (MRL) under the *Pest Control Products Act* for the purposes of the adulteration provision of the *Food and Drugs Act*. Health Canada sets science-based MRLs to ensure the food Canadians eat is safe.

Regalia Maxx Biofungicide Liquid Concentrate contains an extract from the giant knotweed, *Reynoutria sachalinensis*, a plant that has a long history of use as a food item and in medicinal products without any reports of adverse effects in the published literature. Levels of exposure from food residues resulting from the use of Regalia Maxx Biofungicide Liquid Concentrate would be significantly lower than the levels people are exposed to when they consume this plant

as a food component or for its health benefits. Also, given that the active ingredient is expected to be non-persistent in the environment, and the low toxicity profile of the ethanolic extract of ground dried plant material, no crop residue data are needed and the establishment of an MRL for the ethanolic extract of *Reynoutria sachalinensis* will not be required by PMRA to ensure safe consumption of treated food commodities.

There are no established Codex MRLs for the ethanolic extract of *Reynoutria sachalinensis* and this active ingredient is also exempt from the requirement of a food tolerance in the United States.

3.4 Aggregate Exposure

The potential for dietary exposure of the general public to the ethanolic extract of *Reynoutria sachalinensis* residues resulting from the use of Regalia Maxx Biofungicide Liquid Concentrate is not expected to be of toxicological concern, considering the low exposure and low toxicity profile of the active ingredient. Exposure via drinking water is also expected to be negligible from the use pattern. Non-occupational (i.e., residential) exposure is not expected because there are no domestic uses or any other registered uses for extract of *Reynoutria sachalinensis*.

The general public is exposed directly to the active ingredient if they consume the source plant for food or for medicinal purposes. In comparison to such direct exposures, the contribution of residue exposure resulting from application of Regalia Maxx Biofungicide Concentrate is expected to be low. As no appreciable increase in dietary exposure is expected to occur from the use of Regalia Maxx Biofungicide Liquid Concentrate, the PMRA has determined that there is no unacceptable risk of harm expected from the aggregate exposure to the extract of *Reynoutria sachalinensis*.

3.5 Incident Reports

Since 26 April 2007, registrants have been required by law to report incidents, including adverse effects to health and the environment, to the PMRA within a set time frame. Information on the reporting of incidents can be found on the Health Canada website. Incidents from Canada and the United States were searched and reviewed for products containing the ethanolic extract of *Reynoutria sachalinensis*.

As of 8 June 2011, there were no health-related incident reports summarized by the United States Environmental Protection Agency or the California Department of Pesticide Regulation for end-use products containing this active ingredient. A search of the publicly available literature and toxicology database indicated no reports of adverse health effects from the biopesticidal or other agricultural uses of *Reynoutria sachalinensis* from the countries where it is authorized for use on crop plants.

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

Reynoutria sachalinensis (a.k.a. giant knotweed) is a native plant in Asia, where it is also intentionally grown for food and animal feed. It also appears in Europe and North America, including Canada, where it is considered an invasive species. The plant can grow in very dense stands along waterways. The active ingredient in Regalia Maxx Biofungicide Liquid Concentrate fungicide is an ethanolic extract of the roots, shoots, and stems of *R. sachalinensis*. As it is a naturally occuring constituant of a plant, this active ingredient is expected to break down completely within a relatively short period of time and, therefore, will not be persistent in the environment.

4.2 Effects on Non-Target Species and Risk Characterization

The environmental risk assessment integrates the environmental exposure and ecotoxicology information to estimate the potential for adverse effects on non-target species. This integration is achieved by comparing exposure concentrations with concentrations to which adverse effects occur. Estimated environmental exposure concentrations (EECs) are concentrations of pesticide in various environmental media, such as food, water, soil and air. The EECs are estimated using standard models which may take into consideration the application rate(s), chemical properties and environmental fate properties, including the dissipation of the pesticide between applications. Ecotoxicology information includes acute and chronic toxicity data for various organisms or groups of organisms from both terrestrial and aquatic habitats including invertebrates, vertebrates, and plants. Toxicology endpoints in risk assessments may be adjusted to account for potential differences in species sensitivity as well as varying protection goals (i.e., protection at the community, population, or individual level). If the generation of quantitative data is not practical for a particular active ingredient/product, a qualitative assessment may be more appropriate.

The risk assessment for extract of *R. sachalinensis*, based on the proposed uses for Regalia Maxx Biofungicide Liquid Concentrate, is qualitative. This is due to the unique, non-toxic mode of action of the active ingredient, and that the plant from which the active ingredient is extracted can be found growing prolifically in various regions of North America, including Canada. This section will present a summary of information concerning the potential effects on non-target species, and will consider an estimate of the exposure.

It has been reported that *R. sachalinensis* is used naturally as a food source by several species of insects, birds, and mammals in the regions where this plant grows. Information provided by the applicant indicates that certain insects (in field observations) will feed on the plant leaves. Honeybees and other pollinators have also been noted to use its pollen and nectar, with no apparent adverse effects. In laboratory studies, extract of *R. sachalinensis* was found to be harmless to the parasitic hymenoptera *Trichogramma cacoeciae,* the predatory mite *Typhlodromus pyri* and the parasitic hymenoptera *Aphidius rhopalosiphi.*

As the active is extracted from the whole plant it is assumed that it is also found in the seeds. As indicated above, birds have been observed consuming the seeds in the environment. Additionally, as this plant extract has a non-toxic mode of action (to plants and the target pathogens) and studies indicated practically no toxicity to other non-target organisms that were tested, birds exposed to food items containing extract of *R. sachanlinensis* are not likely to show adverse effects.

The toxicity of the active ingredient has been assessed by the United States Environmental Protection Agency for mammals and shows practically no toxicity. This is in agreement with the fact that giant knotweed is used by cattle and humans for food with no observed adverse effects.

Toxicity of extract of *R. sachalinensis* to terrestrial plants is not expected as its mode of action is the induction of resistance of the plant to fungal infections. None of the efficacy trials that have been conducted on various crops plants, such as ornamental plants, cereal grains, curcubits, fruiting vegetables, grapes, and strawberries, have shown any signs of crop injury.

Therefore, the use of Regalia Maxx Biofungicide Liquid Concentrate is not expected to pose an unacceptable risk to non-target terrestrial organisms.

The following aquatic exposure scenario is also considered to support the expectation that extract of *R. sachalinensis* will not pose unacceptable risks to non-target organisms in the environment through the proposed uses of Regalia Maxx Biofungicide Liquid Concentrate.

R. sachalinensis plants can grow in very dense stands (estimated natural yield could be >20 tons/year/ha) and are commonly found throughout North America along rivers and stream channels. In this situation, when the plants die back in the fall, due to cold and frost, large amounts of leaf material and exudates could be naturally released into adjacent waterbodies where fish and aquatic invertebrates will be exposed. When compared to the maximum single application rate of 750 mg a.i./ha for Regalia Maxx Biofungicide Liquid Concentrate (equivalent to 2.7 g of dry plant material/ha), the estimated "naturally-occurring" concentration of plant material and exudates would greatly exceed the concentrations that would occur even from a direct application of this product to a stream or pond. Even many repeat applications would not present the same exposure.

The proposed use scenario would not result in a direct application to water. According to the American Society of Agricultural Engeneering (ASAE), the amount spray drifting 1 meter downwind of the application site would be 11% of the application rate (Wolf and Caldwell, 2001), thus reducing even more the amount of active ingredient falling onto an adjacent water body.

As such, the use of Regalia Maxx Biofungicide Liquid Concentrate is not expected to pose an unacceptable risk to non-target aquatic organisms.

5.0 Value

5.1 Effectiveness Against Pests

5.1.1 Acceptable Efficacy Claims

A total of 45 trials were submitted to support disease claims on several crops and crop groups. Some trials tested United States products Milsana or Regalia SC (5% extract of *Reynoutria sachalinensis*) to test efficacy. Data were deemed acceptable if tested rates were the same as the proposed Canadian rates.

Extrapolation of uses with a product that induces ISR is very difficult. Evidence is required to show that the same defence mechanisms are induced in all or most plants in the crop group to make extrapolation valid with this mode of action.

5.1.1.1 Ornamental plants

Powdery mildew: Four trials were conducted in shade houses or greenhouses on gerbera daisy and poinsettia between 2001 and 2010 were submitted to support the claim of control of powdery mildew. Regalia Maxx Biofungicide Liquid Concentrate demonstrated excellent powdery mildew control in one trial, but only partially suppressed the disease in the other trials. The pathogen species was not identified in any trials; however *Oidium* has been identified as pathogenic against both gerbera daisy and poinsettia, as well as many other ornamental plants. Based on the weight of evidence, the claim of suppression of powdery mildew (*Oidium* spp.) on annual and perennial flowering plants including African (gerbera) daisy and poinsettia is supported at the rates proposed.

5.1.1.2 Cereals

Septoria leaf blotch: Four trials conducted on wheat in France and Germany in 2009 were submitted to support the claim of control of septoria leaf blotch. Regalia Maxx Biofungicide Liquid Concentrate demonstrated control of disease symptoms early in epidemics when disease pressure was low; however, the weight of evidence indicates that Regalia Maxx Biofungicide Liquid Concentrate partially suppresses disease symptoms. As only one pathogen was tested in the trials (*Septoria tritici*), the claim will be restricted to that pest. The registrant requested the claim on the entire cereals crop group. Only one crop (wheat) was tested in the trials; therefore, the claim is supported on wheat only. The claim of partial suppression of septoria leaf blotch (*Septoria tritici*) on wheat is supported at the rates and timings proposed.

5.1.1.3 Grapes

Powdery mildew: A total of seven trials conducted in Canada, the United States, France and Chile between 2000 and 2010 were submitted to support the claim of control of powdery mildew. The reviewed data indicates that Regalia Maxx Biofungicide Liquid Concentrate will consistently partially suppress powdery mildew symptoms on grape leaves and fruit under high disease pressure. Plots treated with the commercial standards showed suppression of the same symptoms in the trials, likely due to the high levels of disease expressed in the trials. It is recognized that Regalia Maxx Biofungicide Liquid Concentrate would likely express higher levels of control under lower disease pressures. Therefore, the claim of suppression of powdery mildew (*Uncinula necator*) on grapes is supported at the rates proposed.

Botrytis bunch rot: Five trials conducted in Italy, France, Chile and British Columbia between 2009 and 2010 were submitted to support the claim of control of botrytis bunch rot. One trial was considered as supplementary data as the rates applied were lower than proposed. One additional trial was considered as supplementary data as well because the rate applied in the trial was too high. The trials demonstrate partial suppression of botrytis bunch rot (grey mould) symptoms under moderate to high disease pressure when treated with Regalia Maxx Biofungicide Liquid Concentrate at the proposed rate. The results are comparable to the registered biological product, Serenade (*Bacillus subtilis*), which is registered for suppression of bunch rot. Based on the performance of Regalia Maxx Biofungicide Liquid Concentrate in the trials and comparison to the reference product, the claim of suppression of botrytis bunch rot (*Botrytis* cinerea) on grapes is supported at the proposed rate.

5.1.1.4 Fruiting Vegetables

Bacterial blight: Three trials conducted in Florida between 2008 and 2009 were submitted to support the claim of control of bacterial blight. One trial was considered as supplementary data as Regalia Maxx Biofungicide Liquid Concentrate was tank mixed with another product. Trial results indicate that Regalia Maxx Biofungicide Liquid Concentrate suppresses bacterial leaf spot (*Xanthamonas campestris* var. *vesicatoria*) on tomatoes. *Xanthamonas campestris* causes leaf spot on all of the proposed crops except for eggplant; however, only one crop was tested in the trials. The claim of suppression of bacterial blight caused by *Xanthamonas campestris* on tomato is supported at the rates proposed.

Grey mould: Seven trials conducted in the United States (Tennessee, Texas, Mississippi), France and Italy between 2002 and 2009 were submitted to support the claim of control of grey mould. All trials were conducted in greenhouses. Trial results indicate that Regalia Maxx Biofungicide Liquid Concentrate will suppress grey mould on tomatoes in the greenhouse. Grey mould occurs on all crops in the fruiting vegetables crop group; however, only one crop was tested in the trials. The claim of suppression of grey mould on field tomato is supported at the rates proposed.

5.1.1.5 Strawberries

Powdery mildew: One trial conducted in Michigan in 2003 was submitted to support the claim. The trial indicates that Regalia Maxx Biofungicide Liquid Concentrate will suppress powdery mildew on strawberries when applied at the proposed high rate. However, only one trial conducted under low disease pressure was submitted to support the claim. Based on the results of the trial and the value of the registration, the claim of suppression of powdery mildew (*Sphaerotheca macularis*) on strawberries is conditionally supported. Additional information is required to confirm efficacy.

5.1.1.6 Cucurbits

Powdery mildew: Nine trials conducted in the United States between 1999 and 2009 were submitted to support the claim of control of powdery mildew. One trial was not reviewed as the rate applied was much lower than that proposed (0.0025% v/v). The submitted trials indicate that Regalia Maxx Biofungicide Liquid Concentrate will suppress powdery mildew on cucurbits at the proposed rates. The results are comparable to non-conventional fungicides registered for suppression or control of this disease, but conventional fungicides provided significantly higher levels of control. Although the extrapolation of use claims to other crops is difficult with ISR mode of action, efficacy was demonstrated on multiple crops in the trials. It is assumed that the same or similar activity is being induced in the cucurbit crop group by application of Regalia Maxx Biofungicide Liquid Concentrate. Based on the reviewed evidence, the claim of suppression of powdery mildew on cucurbits is supported at the rates proposed.

5.1.1.7 Greenhouse uses

Efficacy data reviewed in support of the use claims, as indicated above, also supports greenhouse uses.

5.2 Economics

No market analysis was done for this application.

5.3 Sustainability

5.3.1 Survey of Alternatives

The chemical fungicides listed in Table 4 are registered for control or suppression of diseases on the crops found on the Regalia Maxx Biofungicide Liquid Concentrate label.

5.3.2 Compatibility with Current Management Practices Including Integrated Pest Management

The submitted data demonstrated that Regalia Maxx Biofungicide Liquid Concentrate can be used in combination with other conventional and non-conventional fungicides in alternation programs without compromising the efficacy of Regalia Maxx Biofungicide Liquid Concentrate or causing any phytotoxic effects to crops.

5.3.3 Information on the Occurrence or Possible Occurrence of the Development of Resistance

Treatment of cucumber plants with extract of *Reynoutria sachalinensis* was shown to induce the accumulation of eight different phenolic compounds with antifungal activity. Treatment of wheat plants resulted in elevated levels of reactive oxygen species (ROS), which have been shown to restrain pathogen growth. Although not all crops have been examined to characterize ISR reactions, the data implies that resistance mechanisms are being triggered in the tested plants which have a deleterious effect on plant pathogens. It would be difficult for pathogens to develop resistance mechanisms to multiple phenolic compounds and ROS. The development of pest resistance is not expected.

The Fungicide Resistance Action Committee (FRAC) currently classifies certain compounds as having a mode of action of Host Plant Defence Induction (Group P Fungicides); however, extract of *Reynoutria sachalinensis* is not listed as one of these compounds.

5.3.4 Contribution to Risk Reduction and Sustainability

Regalia Maxx Biofungicide Liquid Concentrate is a biological product with a low risk of pest resistance development. This product is compatible with other conventional and non-conventional fungicide treatments for the labelled crops. The active ingredient is effective in suppressing fungal diseases and is an alternative to chemical treatments for organic producers or conventional growers.

6.0 Pest Control Product Policy Considerations

6.1 Toxic Substances Management Policy Considerations

The management of toxic substances is guided by the federal government's Toxic Substances Management Policy, which puts forward a preventive and precautionary approach to deal with substances that enter the environment and could harm the environment or human health. The policy provides decision makers with direction and sets out a science-based management framework to ensure that federal programs are consistent with its objectives. One of the key management objectives is virtual elimination from the environment of toxic substances that result predominantly from human activity and that are persistent and bioaccumulative. These substances are referred to in the policy as Track 1 substances.

During the review process, extract of R. *sachalinensis* was assessed in accordance with the PMRA Regulatory Directive DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management* Policy. Extract of R. *sachalinensis* was evaluated against the following Track 1 criteria: persistence in soil ≥182 days; persistence in water ≥182 days; persistence in sediment ≥365 days; persistence in air ≥2 days; bioaccumulation log K_{ow} ≥5 or BCF ≥5000 (or BAF ≥5000). In order for extract of R. *sachalinensis* to meet Track 1 criteria, the criteria for both bioaccumulation and persistence (in one media) must be met. The technical product and end-use product, including formulants, were assessed against the contaminants identified in the *Canada Gazette*, Part II, Volume 139, Number 24, pages 2641–2643: *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern, Part 3 Contaminants of Health or Environmental Concern.* The PMRA has reached the following conclusions:

- Extract of *R. sachalinensis* is a naturally occurring substance that has a non-toxic mode of action and is not expected to be persistent or bioaccumulative in the environment. For these reasons, exract of *R. sachalinensis* is not expected to be a TSMP Track-1 substance.

- Extract of *R. sachalinensis* is not known to form any transformation products that meet the Track 1 criteria.

- There are no Track 1 formulants or contaminants in the technical product and the end-use product Regalia Maxx Biofungicide Liquid Concentrate.

6.2 Formulants and Contaminants of Health or Environmental Concern

During the review process, formulants and contaminants in the technical are assessed against the formulants and contaminants identified in the *Canada Gazette*, Part II, Volume 139, Number 24, pages 2641–2643: *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern*. This list of formulants and contaminants of health and environmental concern are identified using existing policies and regulations including: the federal Toxic Substances Management Policy; the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act* (substances designated under the Montreal Protocol); and the PMRA Formulants Policy as described in the PMRA Regulatory Directive DIR2006-02, *Formulants Policy and Implementation Guidance Document*. The *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* is maintained and used as described in the PMRA Notice of Intent NOI2005-01, *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern under the New Pest Control Products Act*.

The *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* consists of three parts:

- Part 1: Formulants of Health or Environmental Concern;
- Part 2: Formulants of Health or Environmental Concern that are Allergens Known to Cause Anaphylactic-Type Reactions; and
- Part 3: Contaminants of Health or Environmental Concern.

The contaminants to which Part 3 applies meet the federal Toxic Substances Management Policy criteria as Track 1 substances, and are considered in section 6.1. The following assessment refers to the formulants and contaminants in Part 1 and Part 2 of the list.

Extract of *Reynoutria sachalinensis* does not contain any formulants or contaminants of health or environmental concern identified in the *Canada Gazette*, Part II, Volume 139, Number 24, pages 2641–2643: *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern*.

7.0 Summary

7.1 Human Health and Safety

The available information for the extract of *Reynoutria sachalinensis* and Regalia Maxx Biofungicide Liquid Concentrate is adequate to qualitatively identify the toxicological hazards that may result from human exposure to the end-use product.

The plant extract is likely to be of low acute toxicity via the oral, dermal and pulmonary routes, minimally irritating to eyes and skin, and not a dermal sensitizer. The end-use product is of low acute toxicity by oral, dermal, and inhalation routes, moderately irritating to eyes, mildly irritating to skin, and is not a dermal sensitizer. Since *Reynoutria sachalinensis* has a long history of use as a food component and for health benefits, in some parts of the world, without any reported adverse effects, it is unlikely that the plant extract is carcinogenic, genotoxic, neurotoxic, and/or a developmental/reproductive toxicant.

Occupational exposure to Regalia Maxx Biofungicide Liquid Concentrate is expected to be minimal if the precautionary statements and required personal protective equipment on the product label, which are intended to minimize worker exposure, are observed. As the commercial application involves only authorized personnel, bystander exposure is expected to be negligible. To mitigate the potential of post-application exposure, restricting entry/re-entry until the spray is dried is required.

The dietary risk from food residue exposure resulting from the end-use product application is considered negligible. The PMRA did not require a maximum residue limit (MRL) to be established for extract of *Reynoutria sachalinensis*.

There have been no reports of adverse health effects from the biopesticidal or other crop uses of extract of *Reynoutria sachalinensis* from the countries where it is authorized for such uses.

7.2 Environmental Risk

Extract of *Reynoutria sachalinensis* (a.k.a. giant knotweed) is not expected to be persistent in the environment.

This plant is a natural food source for many terrestrial invertebrates and vertebrates. It has been shown to be harmless to beneficial arthropods, including predators, parasites and honeybees, to mammals and is not toxic to birds as many species have been found to consume the seeds of the plant. The exposure to aquatic organisms is not likely to be greater than from naturally occurring stands of *R. sachalinensis* in the environment.

The risk to non-target organisms is considered to be negligible when used according to the label.

7.3 Value

The data submitted to register Regalia Maxx Biofungicide Liquid Concentrate are adequate to demonstrate efficacy for use on the supported crops in suppressing the proposed diseases and pathogens. Additional information is required to confirm efficacy against powdery mildew on strawberries.

Regalia Maxx Biofungicide Liquid Concentrate will contribute to Integrated Pest Management (IPM) for many crops by providing a rotational product to growers, ultimately reducing reliance on conventional fungicides. This product will be a valuable tool to organic growers.

Extract of *Reynoutria sachalinensis* was identified as a preferred product on the Canadian Grower Priority database as an intermediate priority for powdery mildew on grapes and strawberries, which were supported for registration.

7.4 Unsupported Uses

Data did not support claims for downy mildew control on cucurbits, or for powdery mildew and early blight control on fruiting vegetables.

8.0 Proposed Regulatory Decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of *Reynoutria sachalinensis* Bioprotectant Technical and Regalia Maxx Biofungicide Liquid Concentrate, containing the technical grade active ingredient extract of *Reynoutria sachalinensis*, to suppress a variety of diseases on field and greenhouse edible crops and ornamentals.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

List of Abbreviations

µg	micrograms
µm	micrometres
A.S.A.E.	American Society of Agricultural Engineer
a.i.	active ingredient
BAF	bioaccumulation factor
BCF	bioconcentration factor
bw	body weight
CAS	Chemical Abstracts Service
DACO	data code
EEC	estimated environmental concentration
EP	end-use product
FRAC	Fungicide Resistance Action Committee
g	gram
ha	hectare(s)
hr	hour(s)
ip	intraperitoneally
IPM	Integrated Pest Management
ISR	Induced Systemic Resistance
IUPAC	International Union of Pure and Applied Chemistry
kg	kilogram
K_{ow}	*n*–octanol-water partition coefficient
L	litre
LC_{50}	lethal concentration 50%
LD_{50}	lethal dose 50%
mg	milligram
mL	millilitre
MAS	maximum average score
MIS	maximum irritation score
MRL	maximum residue limit
N/A	not applicable
NIOSH	National Institute for Occupational Safety and Health
N/R	not required
p*K*a	dissociation constant
PMRA	Pest Management Regulatory Agency
PVC	polyvinyl chloride
ROS	reactive oxygen species
SC	soluble concentrate
TGAI	technical grade active ingredient
TSMP	Toxic Substances Management Policy
UV	ultraviolet
v/v	volume per volume dilution

Appendix I Tables and Figures

Table 1 Summary of acute toxicity and irritative effects information for *Reynoutria sachalinensis* dried powder (100%)

STUDY	SPECIES/STRAIN AND DOSES	RESULTS	SIGNIFICANT EFFECTS/ COMMENTS	REFERENCES
Oral toxicity Gavage	Rat - albino Crl:CD®(SD)IGS BR (5/sex) 5000 mg/kg bw	LD_{50} (♂♀) > 5000 mg/kg bw **Low Toxicity**	There were no treatment-related clinical findings, mortalities or gross necropsy findings.	1773493
Dermal toxicity 24-hour exposure under semi-occlusive dressings	Rat - albino Crl:CD®(SD)IGS BR (5/sex) 2000 mg/kg bw moistened with deionized water	LD_{50} (♂♀) > 2000 mg/kg bw **Low Toxicity**	Erythema was observed on a single female on day 12. No edema.	1773494
Eye Irritation Draize method	Rabbit - New Zealand White (2 ♂, 4 ♀) 89-mg dose (weight equivalent to 0.1 mL) instilled into the lower conjunctival sac of the right eye and left unwashed	Maximum average score (MAS) = 7/110 (at 24, 48, & 72 hrs) Average maximum irritation score (MIS): 12/110 (at 24 hr) **Minimally irritating based on MIS**	Corneal opacity in a single animal and irridial irritation in 2 animals. Positive conjunctival reactions in all animals. Irritation was reversible and completely subsided by day 14 or earlier.	1773496
Dermal Irritation 4-hour exposure Draize method	Rabbit - New Zealand White (3/sex) 500 mg applied to the clipped, intact skin under semi-occlusive dressings	MAS = 0.06/8. (at 24, 48, & 72 hours). MIS: 0.17/8 at 72 hr **Minimally irritating based on MIS**	Minimal erythema was observed in 1 female at 72 hours, which was completely resolved by day 4 of the study. No edema was observed at any time points.	1773497

STUDY	SPECIES/STRAIN AND DOSES	RESULTS	SIGNIFICANT EFFECTS/ COMMENTS	REFERENCES
Dermal Sensitization Modified Buehler method. Test Group: 20 (10/sex) Naïve Control: 10 (5/sex) Positive Control: 10 (5/sex)	Guinea pigs - Hartley albino (topical application) Test Group *Induction phase* 400 mg of test substance moistened with deionized water once weekly for 3 weeks. 6-hr exposure and evaluated at 24 and 48 hours after exposure *Challenge phase* Two weeks after the last induction exposure Positive Control group 50% α-hexyl cinnamaldehyde (HCA) Naïve Control group Dosed only at challenge in the same manner as the Test Group	The sensitization incidence index for the test group was 0% (0/20) following challenge dosing. The sensitization incidence index for the positive control group was 40% (4/10) following challenge dosing. **Negative**	Not a dermal sensitizer	1773498

Table 2 Summary of acute toxicity and irritative effects information for MOI 106 20% Organic (20% *Reynoutria sachalinensis* extract w/w).

STUDY	SPECIES/STRAIN AND DOSES	RESULTS	SIGNIFICANT EFFECTS/ COMMENTS	REFERENCES
Oral toxicity (Up and Down Method) Gavage	Rat – albino Sprague Dawley rats (3♀) 5000 mg/kg bw	LD_{50} (♀) > 5000 mg/kg bw **Low Toxicity**	There were no treatment-related clinical findings, mortalities or gross necropsy findings.	1773569
Dermal toxicity 24-hour exposure under semi-occlusive dressings	Rat – albino Sprague Dawley (5/sex) 5000 mg/kg bw dermally applied to 10% of body surface area	LD_{50} (♂♀) > 5000 mg/kg bw **Low Toxicity**	Dermal irritation was noted at 2 ♂and 4 ♀ dose sites between days 1 and 6.	1773571
Inhalation toxicity 4-hour exposure (nose-only inhalation chamber)	Rat – Sprague Dawley (5/sex) Gravimetric chamber concentration: 2.06 mg/L Mass median aerodynamic diameter: 2.7 µm	LC_{50}: > 2.06 mg/L (♂♀) **Low Toxicity**	Test animals were hypoactive after exposure, but recovered by day-4 post-exposure.	1773572
Eye Irritation Draize method	Rabbit - New Zealand albino (1♂, 2♀) 0.1 mL of the test substance was instilled into the lower conjunctival sac of the right eye and left unwashed. Left eyes served as contralateral controls.	Maximum average score (MAS) = 12/110 (at 24, 48, & 72 hours). Average maximum irritation score (MIS): 28/110 (at 1 hour). **Moderately Irritating** (Based on MIS)	At 1 hour post-instillation, 2 treated eyes exhibited corneal opacity and all three treated eyes exhibited iritis and conjunctivitis. Ocular irritation was resolved by day 7 of the study.	1773573
STUDY	**SPECIES/STRAIN AND DOSES**	**RESULTS**	**SIGNIFICANT EFFECTS/ COMMENTS**	**References**
Dermal Irritation 4-hour exposure Draize method	Rabbit - New Zealand White (3 ♀) 0.5 mL of the test substance applied to the clipped, intact skin under semi-occlusive dressings	Primary irritation score: MAS = 1.7/8 (at 24, 48, & 72 hours) MIS: 2.3/8 (at 30–60 min) **Mildly Irritating** (Based on MIS)	One hour after patch removal, all 3 treated sites exhibited very slight to well-defined erythema and 2 treated sites exhibited very slight edema. By day 10 post-exposure, all animals were free of dermal irritation.	1773574
Dermal Sensitization Buehler method. Test Group: 20 (♀) Naïve Control: 10 (♀)	Guinea pigs - Hartley albino (topical application) Test Group *Induction phase* 0.4 mL of the test substance applied once weekly for 3 weeks	Test animals: 5/20 test sites exhibited very faint erythema (0.5) 24 hours after challenge and irritation persisted at 4 of these sites through 48 hours.	Not a dermal sensitizer	1773575

STUDY	SPECIES/STRAIN AND DOSES	RESULTS	SIGNIFICANT EFFECTS/ COMMENTS	REFERENCES
Positive Control: 10 (♀)	6-hour exposure and evaluated at 24 and 48 hours after completion of each exposure *Challenge phase* 27 days after the first induction exposure Historical positive control α-hexyl cinnamaldehyde (HCA) Naïve Control Dosed only at challenge, in the same manner as the Test Group.	Naïve control group: very faint erythema (0.5) at 1 site 24 and 48 hours after challenge Historical positive control group: 3/10 sites exhibited faint erythema (1.0) 24 hours after challenge, and it persisted at one of these sites through 48 hours **Negative**		

MOI 106 20% organic: identical in composition to the EP

Table 3 Summary of genotoxic effects information for MBI-106-AS (20% *Reynoutria sachalinensis* extract w/w).

STUDY	SPECIES/STRAIN AND DOSES	RESULTS	SIGNIFICANT EFFECTS/ COMMENTS	REFERENCES
Reverse gene mutation assay (Ames Assay)	*S. typhimurium* (TA 98, TA 100, TA 1535, and TA 1537) and tester strain *E. Coli* WP2 uvrA Experiment I 10.0, 31.6, 100, 316, 1000, 2500, and 5000 µg/plate Experiment II 50, 100, 200, 500, 1000, 2000, and 5000 µg/plate (TA 98, TA 100, and TA 1535) and tester strain E. Coli WP2 uvrA 10, 20, 50, 100, 200, 350, 1000, 2000, and 5000 µg/plate (only TA 1537) Each assay was conducted with (S9 mixture) and without metabolic activation and the concentrations were tested in triplicate	Biologically relevant increases of revertant colony numbers were observed only in tester strain TA 1537 at a dose of 100 µg/plate and 316 µg/plate in experiment I with metabolic activation and at doses of 20 up to 200 µg/plate in experiment II with metabolic activation **Positive**	Mutagenic	1999079
Micronucleus Assay (*in vivo*)	Mice (NMRI) 0, 50, 125, and 250 mg/kg bw	No biologically relevant increase of micronuclei was found in any of the dose groups evaluated. **Negative**	Non-mutagenic	1999080

MBI-106-AS: plant extract of *Reynoutria sachalinensis*

Table 4 Alternative Fungicides Registered to Control or Suppress the Supported Pests on ornamental Plants, Wheat, Cucurbits, Tomatoes and Grapes

Crop	Active Ingredient	Resistance Management Group	Pests
Ornamental plants	thiophanate-methyl	1	powdery mildew
	copper	M1	
	sulphur	M2	
	folpet	M4	
	triforine	3	
	captan	M4	
Wheat	mancozeb	M3	septoria leaf spot
	chlorothalonil	M5	
	propiconazole	3	
	tebuconazole	3	
	prothioconazole	3	
	metconazole	3	
	pyraclostrobin	11	
	trifloxystrobin	11	
	azoxystrobin	11	
Cucurbits	chlorothalonil	M5	powdery mildew
	potassium bicarbonate	NC (not classified)	
	Bacillus subtilis	44 (biological)	
	sulphur	M2	
	folpet	M4	
	myclobutanil	3	
	pyraclostrobin	11	
	quinoxyfen	13	
Tomato	copper	M1	bacterial blight
	Bacillus subtilis	44 (biological)	
	chlorothalonil	M5	grey mould
	Trichoderma harzianum	biological	
	boscalid	7	
	pyrimethanil	9	

Crop	Active Ingredient	Resistance Management Group	Pests
Grapes	sulphur	M2	powdery mildew
	dinocap + mancozeb	29 + M3	
	copper	M1	
	folpet	M4	
	myclobutanil	3	
	azoxystrobin	11	
	kresoxim-methyl	11	
	boscalid + pyraclostrobin	7 + 11	
	Bacillus subtilis	44 (biological)	
	quinoxyfen	13	
	metrafenone	U8	
	iprodione	1	botrytis bunch rot
	cyprodinil	9	
	boscalid + pyraclostrobin	7 + 11	
	pyrimethanil	9	

Table 5 Use (label) Claims Proposed by Applicant and Whether Acceptable or Unsupported

Proposed use claim	Supported / Unsupported
Ornamental Plants **Annual and Perennial Flowering Plants** **Powdery mildew, *Oidium spp.*** Rate: 0.125 – 0.25% v/v (1.25 – 2.50 ml/L) Repeat as necessary on a 7- to 10-day interval.	Supported as suppression.
Cereal Grains: Barley, Oat, Pearl Millet, Proso Millet, Rye, Triticale, and Wheat **Septoria Leaf Spot (*Septoria* spp.).** Rate: 0.25% v/v in 400-600 liters water per hectare. Repeat applications in 7- to 14-day intervals	Supported as partial suppression on wheat at the rates and timings proposed against *Septoria tritici*.
Cucurbits: Cantaloupe, Cucumber, Pumpkin, Zucchini, Watermelon, Melon, Muskmelon, and Squash **Powdery Mildew (*Sphaerotheca fuliginea* and *Erysiphe cichoracearum*)** Rate: 0.125 – 0.25% v/v in 500-1000 liters water per hectare. Repeat applications at 7- to 10 day intervals.	Supported as suppression.

Proposed use claim	Supported / Unsupported
Cucurbits: Cantaloupe, Cucumber, Pumpkin, Zucchini, Watermelon, Melon, Muskmelon, and Squash **Downy Mildew (*Pseudoperonospora cubensis*)** Rate: 0.125 – 0.25% v/v in 500-1000 liters water per hectare. Repeat applications at 7- to 10 day intervals.	Not Supported.
Fruiting Vegetables: Tomato, Pepper, Eggplant, Ground Cherry, Tomatillo, and Okra **Bacterial Blight (*Xanthomonas* spp.)** Rate: 0.125 – 0.25% v/v in 400-1000 liters water per hectare. Repeat applications in 7- to 10 day intervals.	Supported as suppression on tomatoes at the rates and timings proposed against *Xanthomonas campestris*.
Fruiting Vegetables: Tomato, Pepper, Eggplant, Ground Cherry, Tomatillo, and Okra **Gray Mold (*Botrytis cinerea*)** Rate: 0.25% v/v in water volume sufficient to provide thorough coverage. Repeat applications in 7- to 10 day intervals.	Supported as suppression on tomatoes.
Fruiting Vegetables: Tomato, Pepper, Eggplant, Ground Cherry, Tomatillo, and Okra **Powdery Mildew (*Sphaerotheca* spp.)** Rate: 0.125 – 0.25% v/v in 400-1000 liters water per hectare. Repeat applications in 7- to 10 day intervals.	Not Supported.
Fruiting Vegetables: Tomato, Pepper, Eggplant, Ground Cherry, Tomatillo, and Okra **Early Blight of Tomato (*Alternaria solani*)** Rate: 0.25% v/v in 400-1000 liters water per hectare. Repeat applications in 7- to 10 day intervals	Not Supported.
Grapes **Powdery Mildew (*Uncinula necator*)** Rate: 0.125 – 0.25% v/v in 500-1500 liters water per hectare. Repeat applications at 7- to 14 day intervals.	Supported as suppression.
Grapes **Botrytis Bunch Rot (*Botrytis cinerea*)** Rate: 0.25% v/v in 500-1500 liters water per hectare beginning at bloom. Repeat applications at bunch closure, veraison and preharvest.	Supported as suppression.
Strawberry **Powdery Mildew (*Sphaerotheca macularis*)** Rate: 0.125 – 0.25% v/v in 500-1000 liters water per hectare. Repeat applications at 7- to 10 day intervals.	Conditionally Supported as suppression.

Proposed use claim	Supported / Unsupported
Leafy Vegetable Crops such as Arugula, Beet, Celery, Chervil, Cilantro, Corn Salad, Cress, Dandelion, Dock, Edible Chrysanthemum, Endive, Fennel, Head Lettuce, Leaf Lettuce, Parsley, Purslane, Radicchio, Rhubarb, Spinach, Swiss Chard, and Watercress **Powdery mildew (*Erysiphe cichoracearum*)** Rate: 0.125 - 0.25% v/v in 500-1000 liters water per hectare. Repeat applications in 7- to 10 day intervals.	Not Supported. Withdrawn by the applicant.
Stone Fruits such as Apricot, Cherry, Nectarine, Peach, Plum, and Prune **Powdery Mildew (*Sphaerotheca pannosa* and *Podosphaera* spp.)** Rate: 0.125 – 0.25% v/v in 500-1000 liters of water per hectare at petal fall, and repeat on a 7-14 day interval.	Not Supported. Withdrawn by the applicant.
Stone Fruits such as Apricot, Cherry, Nectarine, Peach, Plum, and Prune **Brown Rot/Blossom Blight (*Monolinia laxa* and *Monolinia fruticola*)** Rate: 0.125 – 0.25% v/v in 500-1000 liters of water per hectare at early bloom and repeat as necessary through petal fall on a 7-day schedule.	Not Supported. Withdrawn by the applicant.
Greenhouse uses	Supported.

References

A. List of Studies/Information Submitted by Registrant

1.0 Chemistry

PMRA Document Number	Reference
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1773487	1999, Evaluation of the Biological Activity of Milsana for Control of Cucumber Powdery Mildew and Validation of the Bioassay Technique, DACO: 2.13.1,2.13.2,2.13.3 CBI
1773488	1999, Selected Group B Analyses for Dried Planet Material of *Reynoutria sachalinensis*, Lot # 11-89/2A, DACO: 2.14.1,2.14.2,2.14.3,2.14.6 CBI
1773489	2000, Supporting Data to Address Preliminary Analysis of TGAI an Use Product Containing *Reynoutria sachalinensis*, Lot # 11-89/2A, DACO: 2.14.14 CBI
1773490	2009, DACO 2 Chemistry Requirement for the Registration of a Technical Grade of Active Ingredients (TGAI), DACO: 2.14.10,2.14.11,2.14.12,2.14.13,2.14.4,2.14.5,2.14.7,2.14.8,2.14.9 CBI
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1836418	2009, *Reynoutria sachalinensis* Bioprotectant Technical, Sub. 2009-2189, DACO: 2.11.3,2.14.4,2.14.5,2.14.6,2.14.7,2.14.8 CBI
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2029407 2010, Certificate of Analysis, DACO: 2.12.1 CBI

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1773494 1998, Acute Dermal Toxicity Study of Milsana Bioprotectant (Technical Active Ingredient) in Albino Rats, DACO: 4.2.2

1773496 1998, Acute Eye Irritation Study of Milsana Bioprotectant (Technical Active Ingredient) in Albino Rabbits, DACO: 4.2.4

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B. Additional Information Considered

i) Published Information

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